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A MINISWINE MODEL OF HEATSTROKE

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Running Head: Heatstroke in Miniswine

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ABSTRACT

We developed a miniswine model of passive heatstroke, in part, to explain the variable hyper-, normo- and hypokalemia seen in heatstroke victims. After a baseline period (Tamb=26-27°C), anesthetized and instrumented miniswine (n=13, mass=44.6 kg) were ramped to 41-43°C, 60% RH; 13 controls were treated identically, but Tre was maintained at 38°C. Tre of the experimental miniswine rose nearly linearly to 45-46°C until death (approx. 4h). The response patterns of mean arterial pressure, heart rate, plasma K^+ , LPS, Ca^{++}, inorganic phosphate, lactate and a variety of other clinical chemical and physiological variables were determined. An explanation for the variability of plasma K^+ in heatstroke victims was proposed. This model may be useful in characterizing the multisystemic pathology of severe heat injury and be useful for assessing innovative therapeutic regimens.

INDEX TERMS:

Potassium, Calcium, Phosphate, pH, Hyperthermia, LPS, Heatstroke, Swine

Disclaimers

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

In conducting the research described in this report, the investigators adhered to the "Guide for the Care and Use of Laboratory Animals," as prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Research Council.

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INTRODUCTION

Heatstroke is a medical emergency requiring immediate intervention to prevent death. Alterations in plasma potassium ion concentrations change membrane potentials, influence contractility of muscle and may be an important component of the pathophysiology of heatstroke. While plasma K^+ rises during severe exercise, (Knochel, 1990; Knochel, 1992; Knochel, 1996) there are controversies in the literature as to whether the plasma concentrations of K^+, Ca^{++} and inorganic phosphate (Pi) rise, fall or remain unchanged as a result of heatstroke (Ayus & Arieff, 1990; Baxter & Teschan, 1958; Hubbard, 1979; Khogali & Mustafa, 1987; Knochel, 1992; Shapiro & Cristal, 1987) and whether respiratory alkalosis develops prior to metabolic acidosis in heatstroke victims(Boyd & Beller, 1975; Hart *et al.*, 1982; Shibolet *et al.*, 1967).

Heatstroke victims show clinical symptoms resembling those of gram negative sepsis, including circulatory shock, elevated plasma levels of gram negative bacterial lipopolysaccharides (LPS) and cytokines and disseminated intravascular coagulation (Bouchama *et al.*, 1993; Bouchama *et al.*, 1991; Gathiram *et al.*, 1988; Graber *et al.*, 1971). We have previously seen in nonhuman primates during experimental heatstroke that LPS enters the circulation at 42.5-43°C (Gathiram *et al.*, 1987a; Gathiram *et al.*, 1988), probably as a result of two factors: a) a reduced splanchnic blood flow caused by hyperthermia led to ischemic damage to the intestinal wall and leakage of LPS from the lumen (where it is always present) into the circulation at Tc up to 43.5°C (Proppe, 1980), and b) at higher temperatures, direct thermal damage to the gut wall and other tissues (Gathiram *et al.*, 1987b).

This paper describes an experimental model of heatstroke in an animal model with a cardiovascular system similar to that of humans and of sufficient volume to permit serial blood samples and the detection of circulating lipopolysaccharides. (Gathiram *et al.*, 1987c; Gathiram *et al.*, 1988). Miniswine physiology is close to that of humans, is virtually identical biochemically and physiologically to standard swine, and this model has the extremely important advantage of being of manageable adult size (Hannon *et al.*, 1990). We have used this model previously to study exertional hyperthermia (Gentile *et al.*, 1996) and the current study was designed to evaluate its usefulness as a model for passively-induced heatstroke.

MATERIALS AND METHODS

The experimental protocol was approved by the local Institute Animal Care and Use Committee of U.S.A.R.I.E.M. and guidelines regarding humane use of animals were rigorously applied. Miniswine were obtained from Charles River Laboratories and housed and fed in the AAALAC accredited facility at USARIEM for at least one month before use. At the time of the experiment the mean body masses were 44.6 $\pm$ 5.6 Kg and mean ages were 14.3 $\pm$ 1.70 months. They were fed daily with standard minipig chow, had water ad lib, and were inspected regularly by the veterinary staff to ensure healthy status. Fecal flotation examination was made to document the absence of endoparasites.

Anesthesia and Surgery. Isoflurane in 100% oxygen was used at a concentration of 4-5% for induction, followed by 2.5-3% for maintenance. Surgical procedures were carried out under general anesthesia without mechanical ventilation, in a temperature-controlled chamber. A catheter was placed into the

right femoral artery for blood sampling, monitoring blood pressure and the parenteral administration of saline and drugs. If rectal temperature (Tre) fell during these procedures, the pig was warmed passively to a rectal temperature of 38±0.1°C. The effect of isoflurane on the cardiovascular system is believed to be limited, and therefore its effect on heat loss from hyperthermia is expected to be small.

Heat Stress. After baseline measurements were taken for 60 minutes (n=13), the environmental temperature (Tenv) within the chamber was adjusted to 41-43°C and 60% relative humidity for 3-5 hours. From time zero, blood samples (5 ml) were taken every 20 min by sterile technique after removing the "dead volume" in catheter lines. After sampling, the dead volume of blood was then injected back through the catheter into the miniswine, followed by 2 ml of sterile saline. Control animals (n=13) were treated the same except that Tenv was not raised, and Tre was maintained at 38°C. The control animals were not allowed to survive and were euthanized with pentobarbital according to AVMA recommendations. The experimental animals were necropsied (AVMA, 1986).

Blood Samples. For gas determinations, 0.8 ml of blood was collected into 1 ml syringes which had been flushed with heparin, sealed, cooled rapidly on ice and analyzed within 10 minutes. For serum, blood was permitted to clot for 30 min at room temperature, and then centrifuged on a clinical centrifuge for 10 min at 4°C. For plasma LPS determinations, blood was collected into EDTA tubes, placed on melting ice for up to 20 minutes, and then centrifuged for 8 min at 1,500 x g at 0°C. Subsequently, the plasma was removed under sterile conditions in a laminar flow hood and processed immediately. Plasma (150 ul, 0°C) was added to 300 ul of 1.88% perchloric acid at 20°C, briefly vortexed, and incubated for 20 min at 37°C. It was then neutralized with 87 ul of 0.5N NaOH, vortexed 10 sec, and frozen. The

next day it was thawed and centrifuged for 15 min at 3,000 x g at 22°C. An aliquot (50 ul) was added by sterile technique to the wells of a microtiter plate and LPS determined by a recent modification of the colorimetric methodology of the Limulus amebocyte lysate technique (Associates of Cape Cod, Falmouth MA).

Laboratory Analyses. Blood gases, pH and hemoglobin were determined on an AVL 995Hb blood gas analyzer, which automatically corrected for temperature up to 44°C. For Tre>44°C, required temperature corrections of pH, PCO_2, and PO_2 were calculated according to manufacturer's instructions. Hematocrit was determined after centrifugation of blood on a clinical hematocrit centrifuge. Total protein was determined by refractometry with an AOTS refractometer (AO Scientific Instruments). Calcium, magnesium, inorganic phosphate, creatinine, BUN, glucose, lactate and enzymes were determined on a Ciba Corning Express 500 clinical analyzer. Sodium and potassium were determined on an IL943 flame photometer.

Statistics. In order to account for inter-individual variability and, in some cases, small changes in several of the measured parameters from the baseline period, data were converted to changes or percent changes from baseline values, and then analyzed by ANOVA and the Tukey post-hoc test. Absolute results are expressed as mean $\pm$s.d., and the null hypothesis was rejected at $p<0.05$.

RESULTS

Following a short lag time, and during the remainder of the heating period, Tre rose at a constant rate of 1.48°C/hour until death which occurred at 45.6°C $\pm$ 0.5°C (not shown).

Cardiovascular Parameters. Upon heating, the heart rate (HR) rose gradually from a baseline of 116 beats per min (bpm) to a plateau of 130 bpm at Tre

between 38-43°C, then rose rapidly to a peak of over 175 bpm at Tre=44 - 45°C, followed by a sharp decline to death (Figure 1). Mean arterial pressure (MAP) showed no significant change with heating until Tre reached 42°C and then declined until death, with a shoulder at 44-45°C, corresponding to the HR peak. However, when the MAP of 3 animals was compared to its own baseline levels, the MAP rose significantly (*ca.* 20%) upon heating, and then declined as at Tre = 42°C, as occurred in other experimental animals.

Blood Gases, pH and Metabolism. As shown in Figure 2, the respiratory rate remained stable until approximately 41°C, rapidly rose to a peak at 42°C and then declined until death. PCO_2 also remained stable until Tre reached 41°C, then declined slightly to Tre=43°C, and then rose rapidly to more than 400% of baseline at death. Arterial pH remained at 7.45 until Tre=42°C, then became slightly more alkaline, peaked at 43°C, and then declined rapidly to 6.8-6.9 at death.

The initial PO_2 was 480mm Hg due to the inhalation of 97% oxygen (Fig. 3). PO_2 declined slowly as Tre rose, and at 43°C fell rapidly to 200 mmHg at death. Lactate concentration, however, began to rise at 42.5-43°C, despite the high PO_2 at these temperatures.

LPS. LPS concentrations remained at baseline levels until 43.5°C and then rose significantly (Figure 4).

Blood Chemistry. Table I records the general trends among these clinical chemical indices of heat injury. The most interesting and prominent effects of heat stress on blood chemistry were seen in K^+, Ca^{2+}, and phosphate (Pi) (Figure 5). As Tre increased, K^+ rose continuously to values 170-180% of baseline($p<0.001$), while Ca^{2+} and Pi gradually fell to minima at 43.5 and 44.5°C, respectively, and then rapidly rose to near baseline values at death.

Renal Function. The blood urea nitrogen/creatinine ratio (Figure 6) an index of renal function, was stable until 41.5-42°C, and then fell at a constant rate until death.

Enzymes. Upon heating, increases (not shown) occurred only for aspartate amino transferase (AST, continuously rising) and lactic dehydrogenase (LDH, rising shortly before death).

DISCUSSION

LPS. Humans running long distances in warm weather show rises in LPS (Bosenberg *et al.*, 1988) due, in part, to decreased splanchnic blood flow secondary to hyperthermia, sympathetic activation, and/or hypoxia (Gathiram *et al.*, 1989). High concentrations of LPS were correlated with increases in nausea, vomiting, diarrhea and decrements in performance (Brock-Utne *et al.*, 1988). Those symptoms are also induced by direct injection of LPS into humans and animals.(Berczi *et al.*, 1966; Dinarello & Wolff, 1993; Michie *et al.*, 1988)

We previously found in monkeys that during heatstroke, plasma LPS concentrations rose first in the portal vein at approximately 42.5°C and 10-15 min later in the systemic circulation (Gathiram *et al.*, 1988). This supports the view that the LPS originates in the flora of the intestines, and leaks out at a high rate when the blood flow to the gut is substantially reduced or when the gut wall is thermally injured (Fine, 1972; Gathiram *et al.*, 1988). In the current experiments we also found that circulating LPS rises in miniswine during heating, but higher temperatures are required to initiate this response. The reason for this is unclear, but it is possible that the amount of LPS present in the miniswine gut is lower than that of the monkeys since the miniswine were maintained in clean, insect-free AAALAC-

accredited facilities, fed laboratory quality chow, and ventilated with filtered air, while the monkeys were maintained under less clean conditions in family groups, fed fresh fruit and vegetables, and breathed unfiltered air. Since: (1) LPS is present during heatstroke in miniswine, monkeys, and in some clinical studies, (2) anti-LPS antibodies and prior infections protected against heatstroke in monkeys (DuBose *et al.*, 1983; Gathiram *et al.*, 1987b; Gorman & Proppe, 1984), and (3) heat stress protected against LPS challenge (Ryan, 1993; Ryan *et al.*, 1992), it is reasonable to conclude that LPS and cytokines, (Bouchama *et al.*, 1993; Bouchama *et al.*, 1991) may participate in the pathophysiology of heatstroke. Therapeutic interventions for heatstroke therefore should consider anti-LPS and anti-cytokine procedures.

K^+. Although severe exercise often led to hyperkalemia (Sjogaard, 1990), the situation in heatstroke is less predictable. Some heatstroke studies reported hyperkalemia in humans and experimental animals, (Gisolfi *et al.*, 1991; Hubbard, 1979; Hubbard, 1990a; Khogali *et al.*, 1983; Knochel, 1992; Lundvall, 1972; Pettigrew *et al.*, 1974) while others reported hypokalemia (Baxter & Teschan, 1958; Khogali & Mustafa, 1987). This miniswine study shows that hyperkalemia is the *primary* response to heat stress, as previously seen in the rat (Gisolfi *et al.*, 1991). In order to propose a mechanism to explain the reports of normokalemia and even hypokalemia of heatstroke, we note the following in studies on cultured cells:

(1) Heating accelerates Na^+ influx by diffusion and speeds its efflux by the Na^+K^+ATPase pump, but with a net increase in $[Na^+]_i$. (Boonstra, 1984; Bowers Jr *et al.*, 1984; Ruifrok *et al.*, 1985; Ruifrok *et al.*, 1986; Yi, 1979)

(2) However, heating does not markedly increase outward diffusion of K^+. (Willis & Anderson, 1997)

(3) Rather, heat activates the normally inactive K,Cl cotransporter in the plasma membrane, leading to a net loss of intracellular K^+ to the interstitial fluid and the circulation. (Willis & Anderson, 1997)

Generally, hyperthermia causes K^+ to leave cells by both the K,Cl cotransporter and by diffusion through leak channels into interstitial fluid faster than its reuptake by the Na^+K^+ ATPase pump. When these observations on whole cells are considered with the hyperkalemia and renal failure seen here in miniswine, the following model may partially explain the variability in plasma K^+ reported for heatstroke victims:

(1) During initial hyperthermia, the kidney excretes the elevated plasma K^+ into the urine, with additional losses through secretions such as sweat and saliva. However, eventually, the combination of more severe hyperthermia, elevated heart rate, and, perhaps, hypovolemia leads to a drop in blood pressure (Figure 1), which, together with mineralocorticoid secretion, reduces kidney function, (Figure 6) and leads to *primary hyperkalemia* in the heat illness victim (Morimoto, 1987). Furthermore, if hyperthermia should cause some rhabdomyolysis, then K^+ from those cells would also contribute to the hyperkalemia. (Knochel, 1990)

(2) When the patient is treated with an infusion of electrolyte solution, blood pressure would be expected to rise with a partial or complete recovery of renal function, as has been seen following the rehydration of dehydrated rats (Morimoto, 1987). This would cause a net excretion of apparently "excess" K^+ in the plasma and lead to *normokalemia*.

(3) Eventually, cooling procedures would lower core temperatures, which would reduce and eventually stop the activity of the K,Cl cotransporter and the loss of K^+ from cells. The cells, however, now would "sense" a net loss of K^+ from the cytoplasm and operate K^+ membrane transporters at high rates to restore K^+ to normal values by pumping it from the plasma, and by so doing, lead to a *secondary*

hypokalemia. Thus, depending upon the timing of blood samples one could theoretically record hyperkalemia, normokalemia or hypokalemia from a single heatstroke victim. Additionally, hypokalemia could occur from diets containing insufficient K^+, and from K^+ losses due to prolonged sweating.

The consistent rise in plasma K^+ could depolarize membrane potentials, lead to depressed muscle contractility, alter neurotransmitter release at synapses (Cochran, 1995), and have other physiological consequences (Andreoli *et al.*, 1990; Knochel, 1992). Furthermore, a K^+ concentration of *ca.* 8 mEq/l as seen in this model may represent an *actual* rise to *16 mEq/l* in interstitial fluid (Kjellmer, 1961) which could directly effect ventricular fibrillation and cardiac arrest (Bynum *et al.*, 1977).

Patterns of Response to Heat Stress Like humans, not all miniswine showed identical **patterns** in their physiological and biochemical responses to heatstroke. The most variable responses were noted among those that showed the most significant changes: HR, glucose, and pH (Table 1) In accordance with physiological principles, PCO_2 appeared to fall and pH rose when the respiratory rate rose substantially. Likewise, when respiratory rate fell, the PCO_2 rose and the pH fell.

In humans, certain serum enzymes (creatine kinase, AST, aldolase, LDH, and alkaline phosphatase) rise within 5 min of finishing a marathon race (Lijnen *et al.*, 1988), and the cellular injury indicated by these elevations is clearly reversible. Paradoxically, animals heated in the experiment for longer than the duration of a marathon raced showed *lower* or no increases in serum enzymes. Therefore, either a) cellular injury in this heatstroke model is present but takes longer to manifest itself (e.g., induction of cytokines?), b) the injury is present and non-reversible, but a rise in enzyme concentrations is precluded by early death from other causes, (i.e.,

respiratory depression, acidosis, hyperkalemia, etc.), or c) the cells are *not* severely injured and presumably could be restored to normal function with aggressive intervention. In accordance with this last concept, moderate heating reversibly increases intracellular sodium and calcium ion concentrations in cultured cells (Kiang *et al.*, 1992), but when Tamb > 43°C, then the rises become irreversible. (Gaffin *et al.*, 1996; Koratich *et al.*, 1997)

Despite breathing supplemental oxygen, hyperpnea, which was probably thermally driven occurred in these miniswine. This led to an early akalosis that repressed respiration (50%) at pH 7.46, in accordance with physiological principles. The metabolic acidosis observed later can lead to reduced contractility of skeletal and cardiac muscles (Blanchard & Solaro, 1984; El-Saleh & Solaro, 1988). Elevations in magnesium concentration oppose those changes and might be considered for experimental use as potential therapeutic agent (Blanchard & Solaro, 1984).

Our observations on the biphasic alterations in calcium and phosphate concentrations in the miniswine model may explain the previous conflicting observations in heatstroke patients (Shapiro & Cristal, 1987; Shibolet *et al.*, 1976). We found that early hypophosphatemia and hypocalcemia were followed by a late return to control or even overshoot values, possibly explaining the conflicting results in the literature.

Plasma lactate rose long before PO_2 fell, suggesting (Hubbard, 1990b) that glycolysis may be elicited by mechanisms other than insufficient oxygen. It is still possible, however, that despite the presence of adequate oxygen in arterial blood, vasoconstriction caused by A-V shunting around an ischemic core led to the elevated lactate production. However, this hypothesis remains to be tested.

Most of the prominent changes in physiological and biochemical variables occurred at temperatures above 41°C. Therefore, previous explanations for the pathophysiology of heatstroke based on extrapolations from 39.5-40°C may not be relevant. It is interesting to note that the decline in pH occurred close to the Tre (43.0-43.5°C) at which the marked rises in PCO_2 and LPS occurred. Therefore, blood pH may be a useful predictor of the extent of pathology to be expected from a serious heatstroke episode.

Alterations in plasma K^+, PCO_2, pH and LPS in this miniswine model were both temperature- and time-dependent and may be important components of the pathophysiology of heatstroke. Pharmacological agents that reduce cellular potassium leakage or increase Na^+/K^+-pump activity and anti-LPS agents should be considered as possible therapy or prophylaxis.

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LEGENDS

Figure 1. Effect of Hyperthermia on Mean Arterial Pressure (MAP) and Heart Rate (HR) in Anesthetized Miniswine. After 1-hr baseline, environmental temperature was raised to 42-43°C. * = $p<0.05$ compared to controls; # = $p<0.05$ compared to own baseline values.

Figure 2. Effect of Hyperthermia on Respiratory Rate (Resp Rate) , PCO_2 and Arterial pH in Anesthetized Miniswine. Changes from baseline levels. * = $p<0.05$ compared to controls; # = $p<0.05$ compared to own baseline values.

Figure 3. Effect of Hyperthermia on PO_2 and Lactate Concentration in Anesthetized Miniswine. Percent change from baseline level. * = $p<0.05$ compared to controls; # = $p<0.05$ compared to own baseline values.

Figure 4. Effect of Hyperthermia on Arterial Lipopolysaccharide Concentration in Anesthetized Miniswine. Change from baseline level. * = $p<0.05$ compared to controls; # = $p<0.05$ compared to own baseline values.

Figure 5. Effect of Hyperthermia on Arterial Potassium, Calcium and Inorganic Phosphate Concentrations in Anesthetized Miniswine. Percent baseline levels. * = $p<0.05$ compared to controls; # = $p<0.05$ compared to own baseline values.

Figure 6. Effect of Hyperthermia on Renal Function. Percent baseline level. * = $p<0.05$ compared to controls; # = $p<0.05$ compared to own baseline values.

Figure 7. Model of Potassium Concentration Changes. 1) Under normothermic conditions the Na^+K^+ ATPase membrane pump helps balance K^+ lost into the plasma through K^+ "leak" channels. Heat activates the K,Cl cotransporter (Willis & Anderson, 1997) leading to a net loss of K^+ from cells into the interstitial fluid, which eventually enters the plasma, is filtered into the kidney, and excreted in the urine. 2) During severe hyperthermia, as seen in the miniswine model, when hypotension commences, kidney function declines, K^+ excretion is reduced, and leads to a reversible *primary* hyperkalemia. 3) In a heatstroke victim, upon infusion of liters of solution, normovolemia returns, blood pressure rises, and renal function returns to normal, including rapid excretion of the apparently "excess" plasma K^+ lowering the concentration to *normokalemia*. 4) During the cooling process, enabled by elevated sweat rates plus active cooling, the K,Cl cotransporter would be inactivated, and K^+ would leave the cell at reduced rates. The cells, however, would "sense" their reduced concentrations of K^+, and actively transport K^+ from the plasma, leading to a *secondary hypokalemia*.

TABLE I. Physiological and Blood Parameters of Anesthetized Heatstroked Miniswine

Parameter	Baseline Values (± S.D.)	n/N*	Primary Pattern During Heatstroke	Refs. to Similar Patterns in Other Mammals.
MAP	73.5 (15.8) mm Hg	12/13	Stable or rise, then decline with shoulder at 44C	(Kregel *et al.*, 1988)
HR	103.4 (23.2) bpm	8/13	Plateau at 40-43°C then rapid rise to peak and rapid fall	(Kregel *et al.*, 1988)
Na^+	139.4 (3.86) mmol/l	12/13	Small decline, then rapid rise shortly before death	
K^+	3.92 (0.30) mmol/l	13/13	Continuous rise to high values.	(Knochel, 1992)
Ca^{2+}	9.39 (0.73) mg/dl	12/13	Small decline then small rapid rise.	(Shapiro & Cristal, 1987; Shibolet *et al.*, 1976)
LPS	1.12 (0.98) EU/ml	6/7	Stable, then rises rapidly before death	
Mg^{2+}	1.94 (0.44) mEq/dl	4/13	No change	
Pi	6.4 (0.76) mg/dl	7/13	Gradual fall, then rise before the Ca^{++} rise	
Hct	27.8 (1.36) %	12/13	Continuously rising value	
Hb	8.98 (1.09) g/dl	13/13	Continuously rising value	
PCO_2	45.74 (5.37) mm Hg	12/13	Stable, small decline then rapid rise.	
pH	7.42 (0.05)	9/13	Stable, small rise after resp peak, then large fall	
Total Protein	6.27 (0.32) g/dl	8/13	Stable, then small rise before death	
Albumin	3.90 (0.23) g/dl	13/13	No change	
Osmolality	290.4 (3.7) mOsm/kg	12/13	Stable, then gradual rise before death	
Glucose	88.0 (20.6) mg/dl	8/13	Slow rise, then fall before death	
Lactate	16.3 (4.06) mmol/l	11/13	Gradual rise to a plateau, or peaks then falls	
Insulin	8.15 (1.39) u/ml_	6/6	Gradual rise to occasionally high levels before death	
BUN/Creatinine	18.5 (5.99	12/13	Stable to 41°C, then slow fall	
AST	29.4 (7.54) u/ml	9/9	Gradual rise	(Van der Linde *et al.*, 1992)
LDH	299.8 (69.3) u/ml	13/13	Stable, then rise shortly before death	(Van der Linde *et al.*, 1992)
ALT	45.2 u/ml	13/13	No change	(Van der Linde *et al.*, 1992)
CK	197.3 (31.3) u/ml	13/13	No change	(Van der Linde *et al.*, 1992)

* Number of experimental animals actually showing the pattern / Total tested

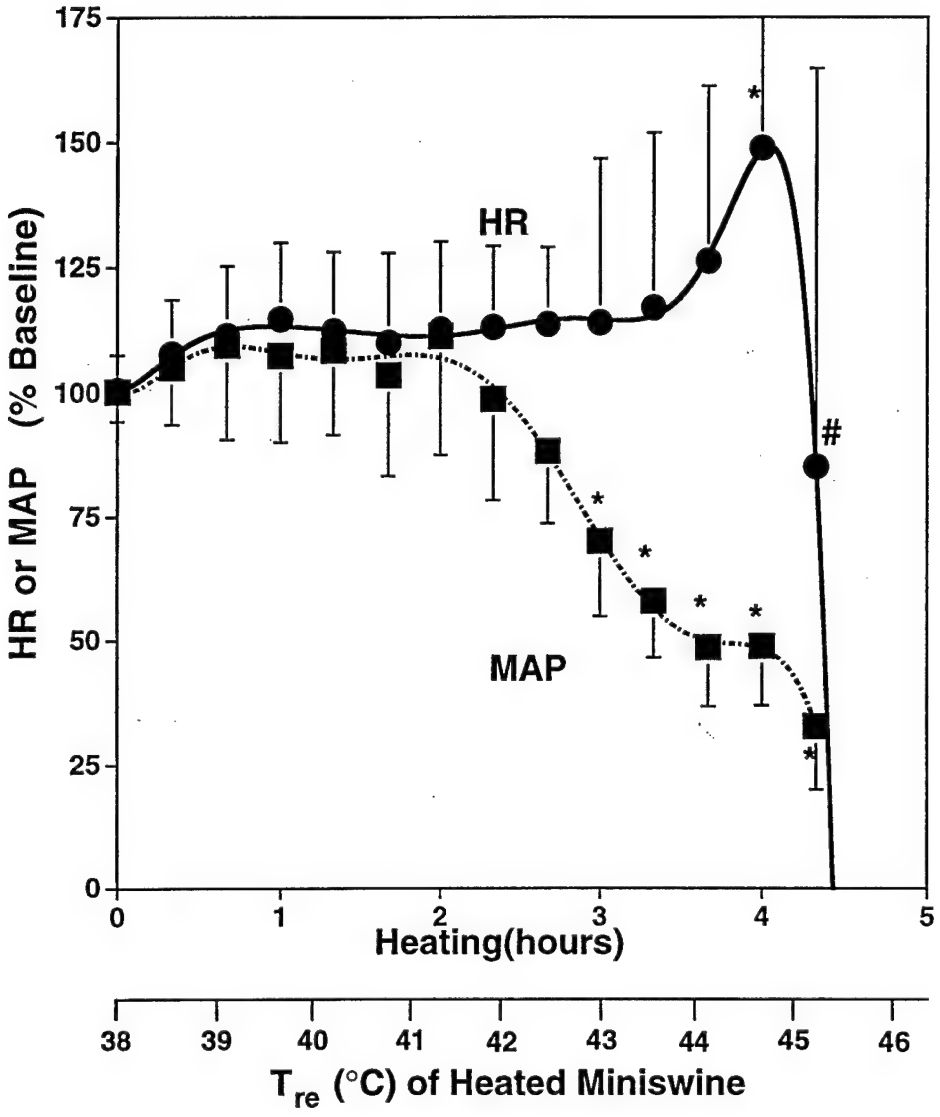
175
150
125
100
75
50
25
0
HR or MAP (% Baseline)
HR
MAP
*
#
0
1
2
3
4
5
Heating(hours)
38
39
40
41
42
43
44
45
46
T_{re} (°C) of Heated Miniswine

Fig 1

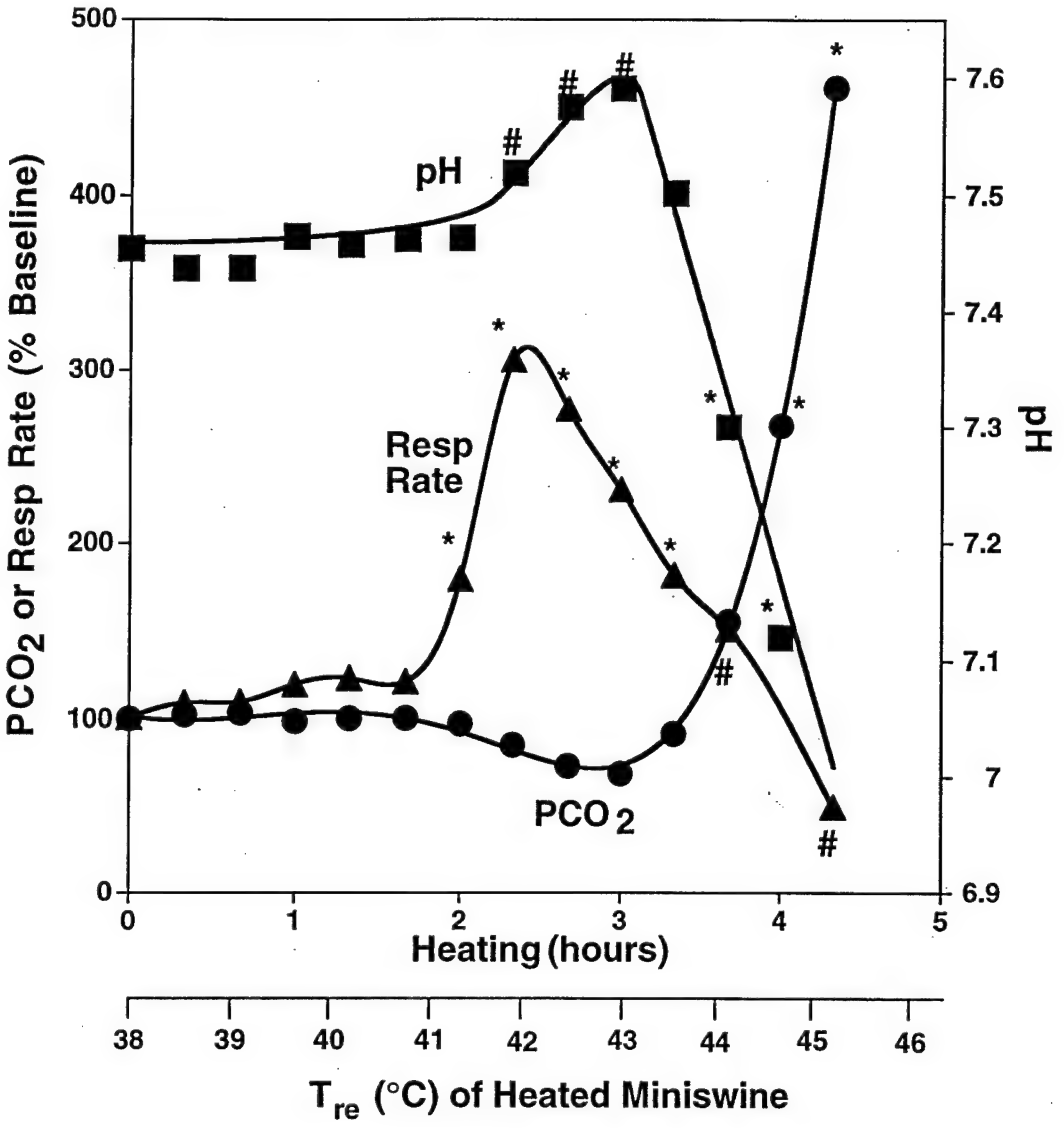
500
400
300
200
100
0
PCO_2 or Resp Rate (% Baseline)
pH
Resp Rate
PCO_2
7.6
7.5
7.4
7.3
7.2
7.1
7
6.9
pH
0
1
2
3
4
5
Heating (hours)
38
39
40
41
42
43
44
45
46
T_{re} (°C) of Heated Miniswine

Fig. 2

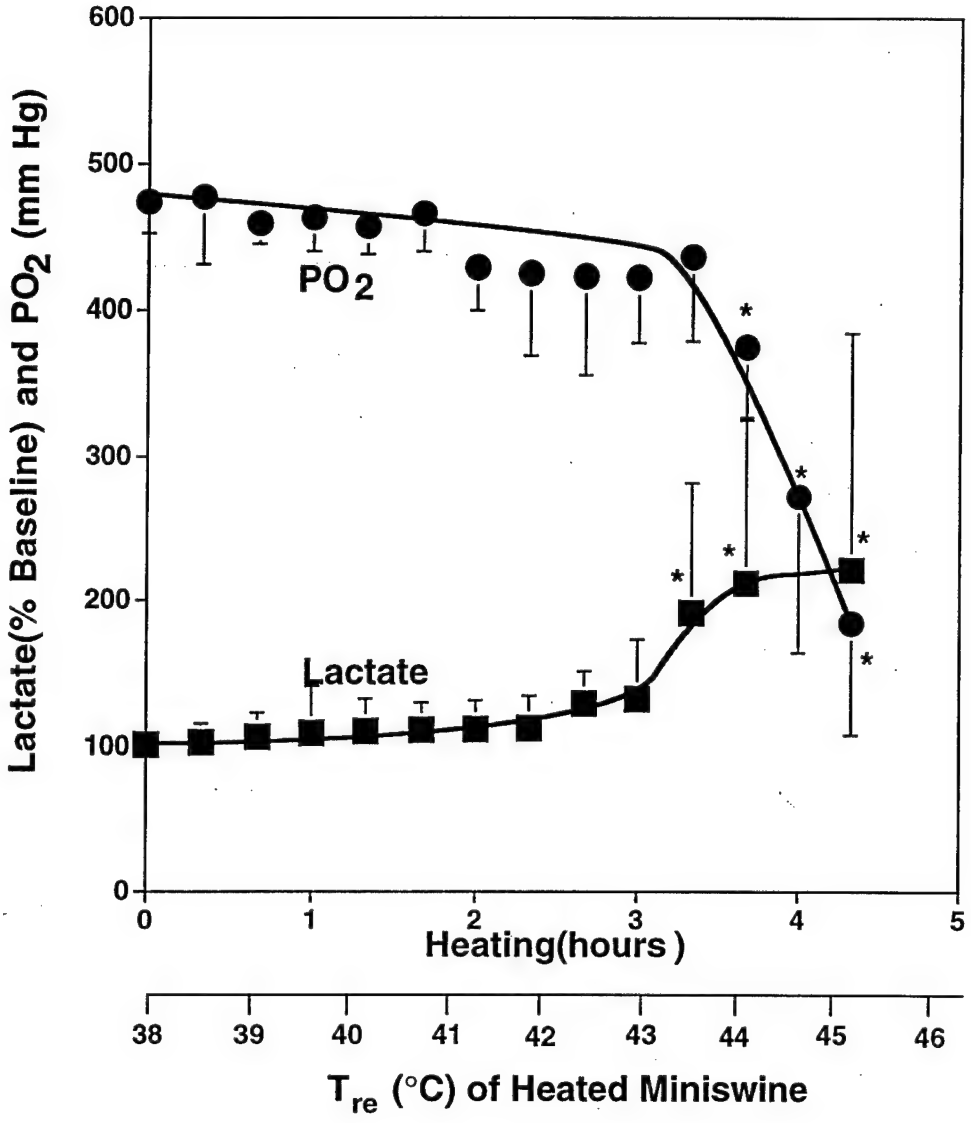
600
500
400
300
200
100
0
Lactate(% Baseline) and PO2 (mm Hg)
PO2
Lactate
*
0
1
2
3
4
5
Heating(hours)
38
39
40
41
42
43
44
45
46
Tre (°C) of Heated Miniswine

Fig. 3

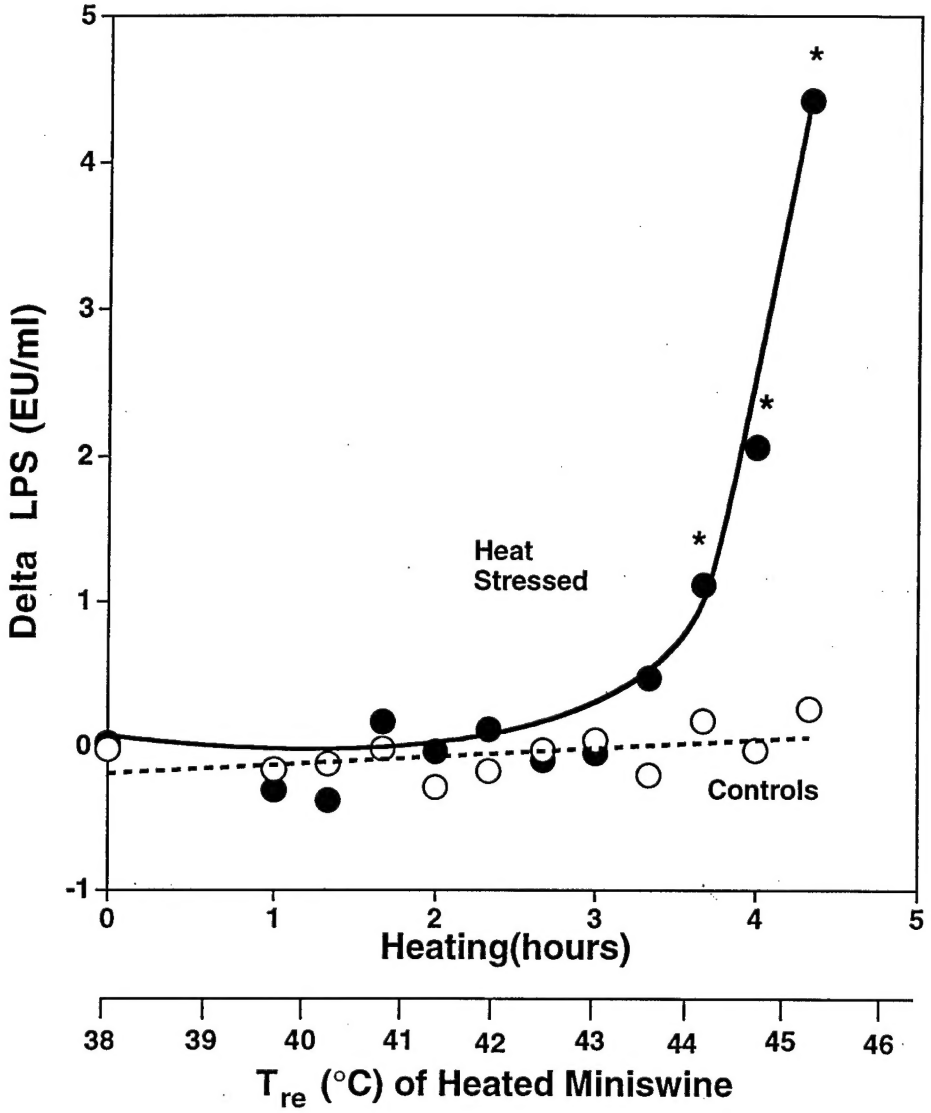
Delta LPS (EU/ml)
5
4
3
2
1
0
-1
*
*
*
Heat
Stressed
Controls
0
1
2
3
4
5
Heating(hours)
38
39
40
41
42
43
44
45
46
T re (°C) of Heated Miniswine

Fig. 4

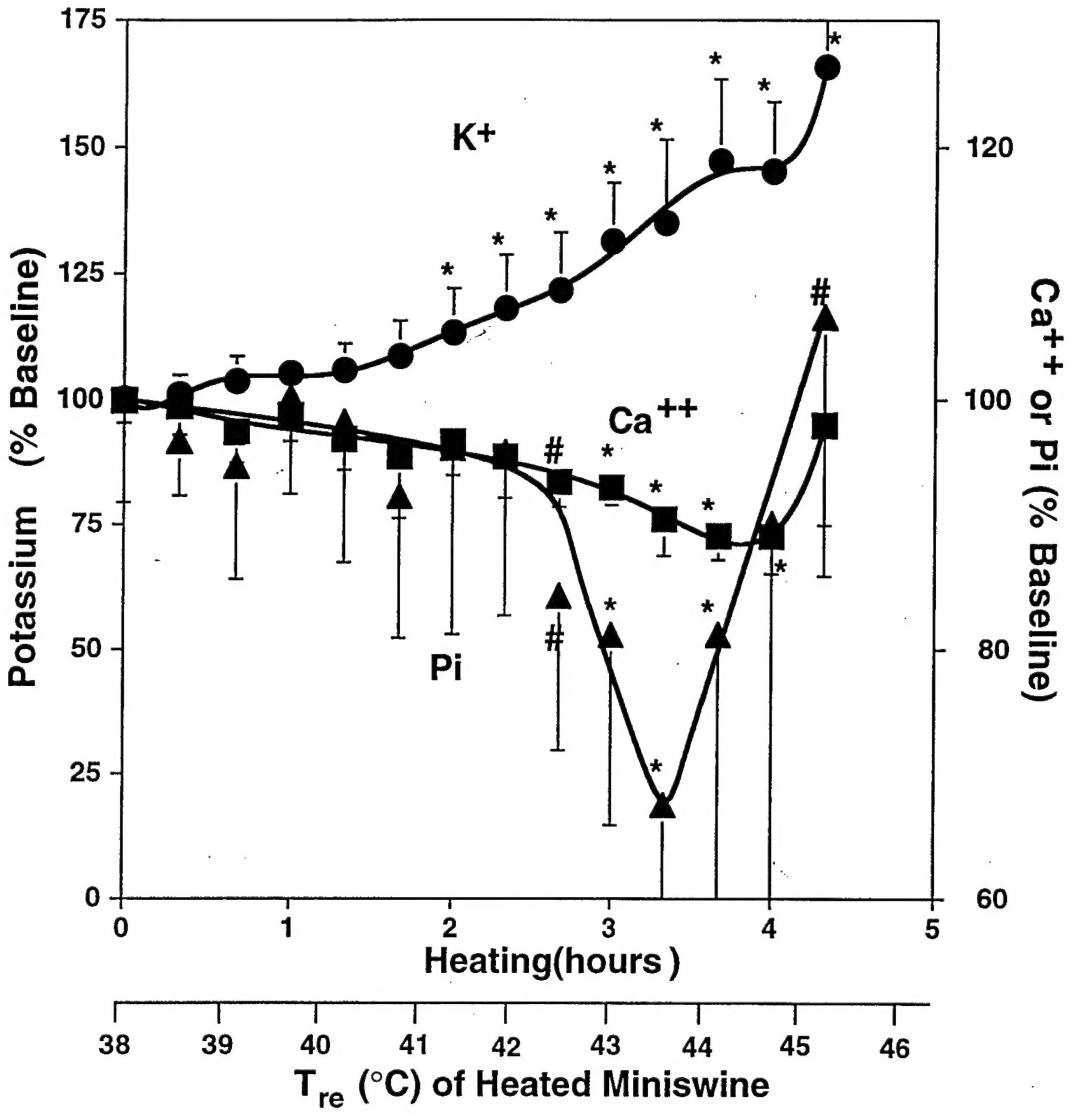
175
150
125
100
75
50
25
0
Potassium (% Baseline)
120
100
80
60
Ca++ or Pi (% Baseline)
K+
Ca++
Pi
0
1
2
3
4
5
Heating(hours)
38
39
40
41
42
43
44
45
46
T re (°C) of Heated Miniswine

Fig. 5

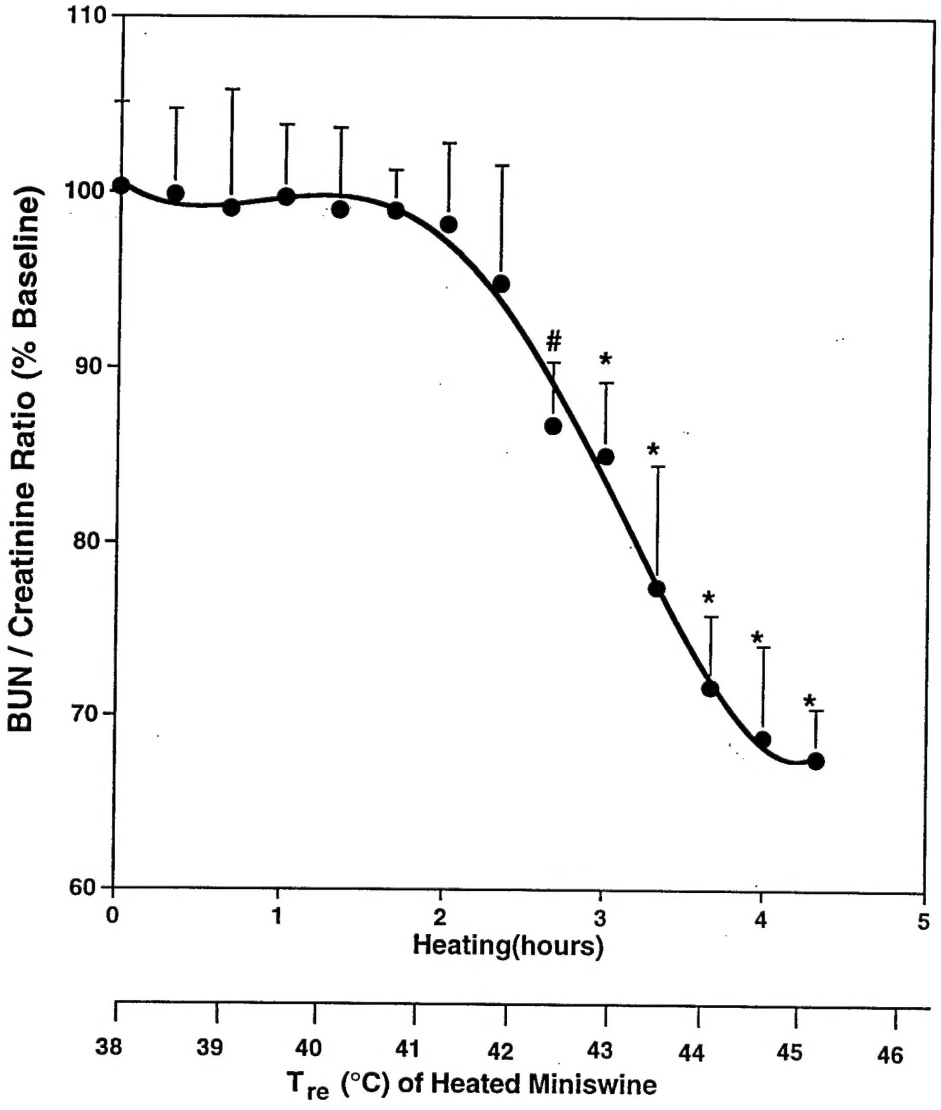
110
100
90
80
70
60
BUN / Creatinine Ratio (% Baseline)
#
*
*
*
*
*
0
1
2
3
4
5
Heating(hours)
38
39
40
41
42
43
44
45
46
T_{re} (°C) of Heated Miniswine

Fig. 6

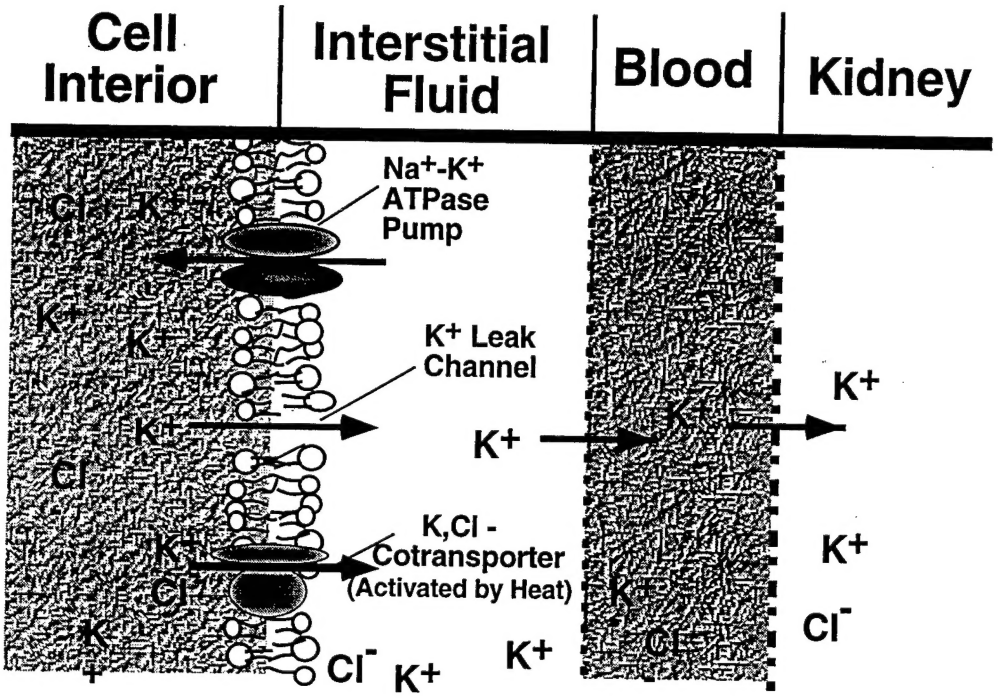
Cell Interior
Interstitial Fluid
Blood
Kidney
Na+-K+ ATPase Pump
K+ Leak Channel
K,Cl - Cotransporter (Activated by Heat)
K+
Cl-

Fig. 7